Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 215-292 are pending in the application, with 215, 231, 245, 261 and 275 being the independent claims.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

The amendment to the specification removes an embedded hyperlink and or browser executable code, accordingly, no new matter has been added by this amendment.

Support for the amendment to claims 231 and 261 adding the limitation "to reduce the severity of anthrax infection," can be found in the specification at paragraphs [0057] and [0116]. Accordingly, no new matter has been added by these amendments.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Response to the Election/Restriction Requirement

On page 2 of the Office Action (hereinafter "OA") the Examiner acknowledged the previous election of group II (claims 174 and 214), with traverse. In the OA the, the Examiner did not find Applicant's arguments persuasive. The Examiner did indicate that fragments and variants of SEQ ID NO:4, for example SEQ ID NO: 2, 6 and 8 will be examined provided the claims are dependent on SEQ ID NO:4.

Information Disclosure Statement

On page 2 of the OA, the Examiner acknowledged the receipt and consideration of an information disclosure statement (IDS), filed September 11, 2006.

The references submitted with the response of September 11, 2006, were submitted in support of Applicant's arguments. The references were not otherwise listed on a separate IDS, with the exception of Exhibits A and B which were filed with the IDS of August 26, 2005.

Objection to the Specification

On page 3 of the OA, the Examiner has objected to the specification. The specification is objected to because it contains an embedded hyperlink and/or other form of browser executable code. Specifically, the Examiner cited paragraph [0067] as comprising an embedded hyperlink. Applicants have amended the specification to remove the embedded hyperlink and/or other form of browser executable code. Accordingly, Applicants request that this objection be withdrawn.

Rejections under 35 U.S.C. § 112

35 U.S.C. § 112, first paragraph (scope of enablement)

The Examiner has rejected claims 215-292 under 35 U.S.C. § 112, first paragraph. (OA at pages 3-15.) The Examiner asserts that the specification while "being enabling to reduce the severity of anthrax infection" in a mammal, does not reasonably provide enablement for a method of preventing anthrax or eliciting an immune response to treat infection. (OA at pages 3-4.)

Applicant respectfully disagrees with the Examiner's position. However, solely in an effort to advance prosecution, and not in acquiescence to any reasoning underlying the Examiner's rejection, claims 231 and 261 have been amended to recite "reduce the severity of anthrax infection," as suggested by the Examiner. (OA at page 3.)

Applicant notes that the Examiner is on the record as saying that "[t]he results show that all codon optimized DNA vaccine formulations had comparable efficacy as compared to commercially available AVA vaccine." (OA at page 9.) The Examiner acknowledges that the DNA based vaccine of the captioned application is as effective as the commercially available, protein based, AVA anthrax vaccine. In other words, Examiner admits that the vaccine works! Thus, Applicant fails to see why the Examiner persists with the line of rejection that the claims are not enabled for preventing anthrax or a method of reducing the severity of anthrax infection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The captioned application has provided working examples in which three species of animals have been immunized with the claimed DNA based vaccine and all three species have mounted an immune response to protective antigen (hereinafter "PA"), using the PA encoding DNA that is human codon optimized. In challenge experiments all animals that were given the DNA based vaccine survived while all control animals died. (OA at page 9, and also specification examples 12, 13 and 16.) Because the animals survived the challenge experiments, Applicant asserts that the captioned

application is enabled for methods of preventing anthrax infection or a method of reducing the severity of anthrax infection.

i. prevention

The Examiner asserts that the specification does not provide a specific definition of the term "prevention." (OA at page 13.) Applicant respectfully traverses this rejection.

Applicant is using the terms "treatment or prevention" in the captioned application consistent with the art recognized use of these terms. "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). (*See* MPEP 2111.01.) The ordinary and customary meaning of a term may be evidenced by a variety of sources, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." (*Id.* at page 1314.) Additionally, the Examiner is reminded that breadth of a claim does not make a claim not enabled or indefinite as long as the scope of the subject matter that is embraced is clear. *In re Miller*, 441 F.2d 689 (CCPA 1971). (*See* MPEP 2173.04.)

Applicant has provided claim definitions for the terms "treatment or prevention" in the captioned application. Specifically, the specification defines the term to prevent or treat, *i.e.* cure, ameliorate, lessen the severity of, or prevent or reduce contagion of infectious disease caused by *B. anthracis*. (*See* specification, paragraph [0057].)

Therefore, the term encompasses a range of outcomes from lessening the severity of the disease to the prevention of infection.

The specification defines that "treatments of a vertebrate" refers to the use of one or more compositions of the present invention to prevent, cure, retard, or reduce the severity of anthrax disease symptoms in a vertebrate, and/or result in no worsening of anthrax disease over a specified period of time. More importantly, the specification is clear that "it is not required that any composition of the present invention provide total immunity to *B. anthracis* or totally cure or eliminate all anthrax disease symptoms." (*See* specification, paragraph [0116].)

A dictionary definition of "preventative" is "to come before, prevent," which is synonymous with "prophylactic." (*See* Steadman's Medical Dictionary, at page 1425, Marjory Sraycar ed., William and Wilkens 1995) (**EXHIBIT A**). Steadman's defines "prophylactic" as "(1.) Preventing disease; relating to prophylaxis. (2.) An agent that acts to prevent disease." (*Id.* at page 1439.) The term "treatment" is defined in Steadman's as "[t]o mange a disease by medicinal, surgical or other measures." Treatment measures in include active, causal, palliative, preventative, prophylactic or symptomatic treatment. (*Id.* at page 1843.) Active treatment refers to "a therapeutic substance or course intended to ameliorate the basic disease problem, as opposed to supportive or palliative."

Examples 12, 13 and 16 of the captioned application describe immunization and challenge experiments in rabbits. Indeed, all animals that were immunized with SEQ ID NO:7, a human codon optimized nucleic acid sequence encoding amino acids 199-764 of SEQ ID NO:4 with a deleted furin cleavage site, and Vaxfectin or DMRIE/DOPE survived anthrax spore challenge as described in Table 17. Applicant has shown that

immunization with an anthrax DNA vaccine can provide protective immunity in animals. (*See* specification Table 17.)

Contrary to Examiners assertion, the definition of the term prevention is provided in the captioned application, and the term is consistent with the art recognized definition found in Steadman's medical dictionary. It is recognized in the art that "[u]ntreated inhalation or gastrointestinal anthrax has a case fatality of essentially 100% while cutanous anthrax has a case fatality of 25%." (*See* Lee *et al.* cited by the Examiner in the 35 U.S.C. 103(a) rejection below.) Because inhalation or gastrointestinal anthrax infection results in 100% fatality in the infected subject, any treatment or prevention measure that reduces the fatality rate to 90, 70, 50, 30, 10 or 0% falls within the scope of treatment or prevention. The specification has shown "prevention," a reduction of the fatality to zero, using the claimed compositions. In the working examples provided, all vaccinated animals survived the inhalation anthrax challenge. Applicant asserts that the term "prevention" is sufficiently defined in the specification for the ordinary artisan to understand the scope of the claimed subject matter. Applicant respectfully requests reconsideration and withdrawal of the rejection.

ii. reducing the severity of infection and prevention

The Examiner alleges that it would require extensive experimentation to carry out the claimed method. (OA at pages 5.) Specifically, the Examiner asserts that the specification fails to provide guidance on "(i) how an artisan of skill would have practiced the claimed method in treating or preventing any form of anthrax infection by administering via any route . . . (ii) the claimed method would have resulted in immune response sufficient to treat or prevent any form of anthrax." (OA at page 5) The

Examiner appears to doubt whether the ordinary artisan would be able to treat or prevent anthrax by administering the vaccine using a route of administration not exemplified in the specification. Applicants respectfully traverse this rejection.

The Examiner is reminded that a claim may encompass inoperative embodiments within the scope of the claim. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); MPEP § 2164.08. Here, Applicant has shown in three animal models that the instantly claimed vaccine formulation induced an immune response in each animal. Applicant has shown that that the vaccine reduces the severity of infection or provides complete protection in the animals when challenged with a lethal dose of anthrax. (*See* specification paragraphs [0239-0248])

Examples 12, 13 and 16 of the captioned application describe immunization and challenge experiments in rabbits. Indeed, all animals which were immunized with SEQ ID NO:7, a human codon optimized nucleic acid sequence encoding amino acids 199-764 of SEQ ID NO:4 with a deleted furin cleavage site, and Vaxfectin or DMRIE/DOPE survived anthrax spore challenge as described in Table 17. Applicant has shown that immunization with an anthrax DNA vaccine can provide protective immunity in at least 40 animals. (*See* specification Table 17.) Additionally, the animals tested were subjected to aerosolized anthrax spore challenge which is "the gold standard for anthrax vaccine efficiency because it exposes the animal to the agent and expected mode of delivery anticipated in the event of a bioterrorist attack." (Hermanson, *et al. Proc. Natl. Acad. Sci.* 101:13601-13606 (2004), at page 13605, document previously listed as NPL4 on IDS submitted August 26, 2006.) "A cationic lipid-formulated plasmid DNA vaccine

confers sustained antibody-mediated protection against aerosolized anthrax spores." (*Id.* at page 13604-13605.)

Applicant asserts that the specification is enabled for methods of preventing or reducing the severity of *B. Anthracis* infection using a composition comprising GAP-DMORIE, a co-lipid and an isolated polynucleotide comprising a codon optimized polynucleotide encoding a polypeptide that is at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4. Applicant respectfully requests reconsideration and withdrawal of the rejection.

iii. effective immune response with 97% identity to SEQ ID NO:4

The Examiner alleges that "[i]t is not apparent from the specification whether any sequence with 97% identity to SEQ ID NO:4 that is optimized for human codon would elicit effective immune response against *Bacillus anthracia* [sic] infection." (OA at page 6.) The Examiner further asserts that "inter specific [sic] difference of codon usage is one of the major obstacles for effective induction of specific immune responses against bacteria by DNA immunization." (OA at page 6.) The Examiner asserts that the artisan practicing the invention would have to carry out undue experimentation as "only optimal codon usage would have provided optimal immune response sufficient for the treatment of *Bacillus anthracia* [sic] *infection*." (OA at page 7.) The Examiner cites Nagata *et al.* in support of the proposition that only optimal codon usage elicits an effective immune response. (OA at page 6.) Additionally, the Examiner asserts that it is not clear that all codons are codon optimized. "[I]n the instant case, it is noted that Applicant's contemplate delivering a composition that recited the term 'wherein about' implying one

more or one less codon in an optimized coding region of SEQ ID NO:4." (OA at page 12.) Applicant respectfully traverses this rejection.

Applicant notes that the Examiner agrees that the skilled artisan would be able to use PA from various strains. "[E]xaminer agrees with the Applicants assertion that 97% sequence identity to the polypeptide would allow one skilled in the art for using PA from various strains of *B. Anthracis*." (OA at page 12.)

Contrary to the Examiners assertion, the claims do not recite a composition having one more or one less codon in an optimized coding region. (OA at page 12/) "The Examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are analyzed individually." (MPEP 2164.08.) Here, the claims clearly indicate that the amino acids spanning 199-764 of SEQ ID NO:4 are codon optimized for the human coding frequency. (*See* specification, table 2, pages 23-26.) The degeneracy in the genetic code provides that some amino acids can be coded for by more than one codon. The claims reflect the probability with which each codon is expected to appear in a human coding sequence. The ordinary artisan would recognize that some variability is permissible without effecting the overall ratio of codon frequency.

The captioned application describes SEQ ID NO:1, a human codon optimized nucleic acid sequence encoding amino acids 199-764 of SEQ ID NO:4 having the intact furin cleavage site. Comparing the human codon optimized PA sequence of SEQ ID NO:1 with the native *B. Anthracis* coding sequence of SEQ ID NO:3 a ~25% difference is noted at the nucleic acid level in the coding sequence that spans the PA region. SEQ ID NO: 1 and SEQ ID NO: 7 are identical with the exception of a 21 nucleotide deletion

in SEQ ID NO:7, corresponding to furin cleavage site. The human codon optimized PA sequence of SEQ ID NO:7 and the native *B. Anthracis* sequence of SEQ ID NO:3 are, therefore, also ~25% different at the nucleic acid sequence level.

As described above, examples 12, 13 and 16 of the captioned application describe immunization and challenge experiments in rabbits, using the human codon optimized nucleic acid sequence of SEQ IS NO:7. Gu *et al.* has shown that a DNA plasmid encoding a non-codon optimized anthrax PA immunogen protects mice from *in vivo* challenge with the lethal toxin. (Gu *et al.* Vaccine 17:340-344 (1999), document AS5 previously provided on an IDS, at page 343, column 1, last paragraph.) Lee *et al.* has shown that a Venezuelan equine encephalitis (VEE) virus construct encoding a non codon optimized DNA PA anthrax immunogen provides protection in mice. (*See* Lee *et al.*, see paragraph [0026], table (1) and [0027]; cited by Examiner in the 35 U.S.C. §103(a) rejection below) Mice inoculated with the VEE replicon particle containing PA produced high specific antibody titers, and the mice were protected from developing anthrax when challenged subcutaneously. (Lee *et al.*, paragraph [0006].) Here, Applicant has clearly shown that a codon optimized nucleic acid sequence encoding PA antigen of *B. Anthracis*, that differs from the native *B. Anthracis* sequence by about 25% at the nucleic acid level, is effective at providing complete protection in animals when subjected to aerosolized anthrax spore challenge. Thus, the ordinary artisan reading the specification in light of what was known in the art at the time the invention was made would recognize that a range of codons at the nucleic acid level is permissible to obtain a protective immune response.

Applicant reiterates that the claimed methods do not require any specific level of immune response other than to reduce the severity or prevent anthrax infection as defined in the specification, *e.g.* at paragraphs [0057] and [0116]. Certainly, the claimed methods do not require an "optimal immune" response as the examiner is requiring. The data in the Nagata *et al.* reference showed some level of immune response in all DNA plasmids tested, including the plasmid which had the native codon usage. (Nagata *et al.*, *Biochem. Biophys. Res. Comm.* 261:445-451 (1999), see Fig. 3.) Moreover, Applicant asserts that based on the teaching in the specification, it would have been routine experimentation for one of skill in the art to test various codon optimized polynucleotides in the mouse, rabbit and primate animal models described in Examples 10-13 and 15 or in the assays described in Example 9 of the present application to determine which variants could treat or prevent anthrax infection.

Examples 12 and 13 of the captioned application describe immunization and challenge experiments in 12 groups of rabbits (10 rabbits in each group) and one group of 4 rabbits (which were immunized with the commercial AVA anthrax vaccine). This is a total sample size of 124 animals, with 10 animals per formulation. Indeed, all animals which were immunized with SEQ ID NO:7, a human codon optimized nucleic acid sequence encoding amino acids 199-764 of SEQ ID NO:4 with a deleted furin cleavage site, and Vaxfectin or DMRIE/DOPE survived anthrax spore challenge as described in Table 17. Applicant has shown that immunization with an anthrax DNA vaccine can provide protective immunity in at least 40 animals. (*See* Table 17.) Additionally, the animals tested were subjected to aerosolized anthrax spore challenge which is "the gold standard for anthrax vaccine efficiency because it exposes the animal to the agent and

expected mode of delivery anticipated in the event of a bioterrorist attack." (Hermanson, *et al. Proc. Natl. Acad. Sci.* 101:13601-13606 (2004) at page 13605.) "A cationic lipid-formulated plasmid DNA vaccine confers sustained antibody-mediated protection against aerosolized anthrax spores." (*Id.* at pages 13604-13605.)

Furthermore, the Examiner acknowledges that one of skill in the art would have been able to use PA from different anthrax strains. (OA at page 12.) Applicant asserts that based on the teaching in the specification, it would have been routine experimentation for one of skill in the art to test various codon optimized polynucleotides in the mouse, rabbit and primate animal models. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

iv. DNA vaccine protection

The Examiner alleges that it would not be known whether a DNA vaccine provides long term effects. Specifically, the Examiner asserts that the specification does not provide sufficient guidance for the ordinary artisan to infer that "any form of anthrax infection can be treated or prevented by administering codon optimized DNA vaccine via any route such that it elicit an immune response that is effective for long enough for sustained period of time that would have beneficial effects in preventing or treating anthrax infection." (OA at page 7.) The Examiner asserts that "[t]he specification does not provide any specific guidance to overcome this art recognized limitations of dose, type and route of anthrax infection and levels of antibody optimal for protection or treatment in any subject." (OA at page 8.) The Examiner asserts that "the method recited in independent claims are enabled only if instant method elicit optimal immune

response against anthrax infection." (OA at page 15.) Applicant respectfully traverses this rejection.

The Examiner is reminded that the Applicant need not have actually reduced to practice each and every permutation of their claimed invention.

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of **no more effort than is normally required in the art**. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). (S*ee* MPEP 2164.08(b)) (emphasis added).

Example 16 of the captioned application disclose long-term immune response studies in DNA immunized rabbits. Here, 10 rabbits were immunized three time with VR6292 (a plasmid encoding human codon optimized full length PA with the deleted furin cleavage site). The rabbits were observed for 42 weeks following the first injection, and the rabbits immune response was periodically assayed for anti-PA antibody titer, LetX neutralization titer and protective immune response to anthrax spore challenge "the gold standard." 39 weeks after the first injection the rabbits were challenged by aerosol administration of *B. anthracis* (Ames strain) spores, all rabbits survived. Control animals did not survive. Applicant has shown that immunization of rabbits with VR6292 plasmid has lead to the reduction in the severity of anthrax infection, indeed it has lead to the prevention of anthrax infection since the animals survived the challenge with a lethal dose of anthrax. Because the animals survived, the animals must have mounted a sufficient immune response ("optimal") for the animals not to become ill after challenge with a lethal dose of anthrax. Applicant asserts that based

on the teaching in the specification, it would have been routine experimentation for one of skill in the art to test various codon optimized polynucleotides in the mouse, rabbit and primate animal models, using various inculcations methods, and challenge them with lethal dose in order to determine which composition provide the animal with long term protection. Applicant respectfully requests that the rejection be withdrawn.

iv. DNA delivery

The Examiner asserts that the specification does not provide "any evidence that codon optimized polynucleotide could be delivered by any method using any route that would elicit a therapeutic effective level of sustained immune response that would confer immunity against infection over the full scope of the claims." (OA at page 9.) The Examiner asserts that there is the need for an "optimal immune response" and "optimal codon usage" to treat or prevent anthrax infection in an animal. (OA at page 11-12.) The Examiner asserts that the question is "not whether lipid formulation (as amended) comprising instant composition would elicit immune response, rather question is whether instant composition would elicit immune response to level sufficient to prevent anthrax infection." (OA at page 12.)

The Examiner cites Dass *et al.* for the proposition that lipoplex-mediated gene delivery can be toxic. Cationic lipid-DNA complexes "has shown varying degree of success, primarily due to toxicity associated with these formulations." (OA at page 10.)

The Examiner cites McCulskie *et al.* for the proposition that DNA vaccines are unpredictable and that the art recognizes that the route and delivery of DNA vaccine influences the immune response. "Thus, it is not apparent as to how the skilled artisan would carry over a method encompassing treating or preventing any subject infected

with any form of anthrax infection by administering via any route a composition comprising DNA vaccine formulations of GAP-DMORIE and any co-lipids." (OA at page 10)

The Examiner cites Galloway *et al.* for the proposition that the field of DNA vaccines is a largely unpredictable and experimental field and although progress has been made in the field of DNA vaccines, the desired immune response produced by DNA vaccines continue to be unpredictable and inefficient. (OA at page 7.) Additionally, the Examiner cites Leppla *et al.* to support his assertion that there are numerous uncertainties as to "what would be the optimal concentration of serum antibodies in humans that confers immunity to anthrax." (OA at page 8.) Finally, the Examiner alleges that "a regimen of dose scheduling as disclosed from small animal and primate would not be efficacious to confer immunity in humans." (OA at page 8.) Applicant respectfully traverses this line of rejection.

Applicant respectfully asserts that the Examiner is requiring an unreasonable scope of enablement standard. The Federal Circuit has stated that the PTO has the burden of initially showing that Applicants' disclosure suggests "an inherently unbelievable undertaking or involve[s] implausible scientific principles." *In re Brana*, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995). The documents cited by the Examiner do not meet this burden.

The Examiner cites Dass *et al.* for the proposition that lipoplex-mediated gene delivery can be toxic. (OA at page 9) Applicant disagrees. The post filing reference, co-authored by the inventor, (Ferrari *et al.*, "Development of anthrax DNA vaccines." *Curr. Op. in Mol. Therap.* 6:506-512 (2004) (previously presented as Exhibit D in the

response of September 11, 2006) summarizes various published studies using DNA vaccines formulated with various lipids. Table 1 lists 18 different studies with various antigens and 11 different lipid formulations. Thus, Applicant asserts that lipid formulations are not toxic and useful in DNA vaccines. Indeed the Ferrari *et al.* reference states that "there is extensive preclinical evidence suggesting that cationic lipid-based formulations significantly enhance humoral responses of DNA vaccines." (*Id.* at pages 508-509.)

The Examiner cites McCluskie *et al.* for the proposition that the route of administration of DNA is unpredicatble. Applicant disagrees, McCluskie *et al.* comments on the fact that **many routes actually have been shown to be effective** for DNA delivery in mice. (McCluskie *et al.*, *Molecular Medicine*. 5:287-300, (1999) at page 295, and Fig. 1, (emphasis added).) In mice, five of the eight injection routes of DNA delivery produced serum antibodies as did the gene gun DNA administration. It is noted, in this reference, that the non injected routes did not result in antibody production in mice. (*Id.* at page 295.) It is important to point out that the DNA composition used in McCluskie *et al.*, differ from the instant invention. McCluskie *et al.* used DNA coated onto gold particles diluted in saline, while the present invention is directed to a composition of DNA, GAP-DMORIE and a co-lipid.

Applicant notes that the Galloway *et al.* reference, cited by the Examiner to show the unpredictability of DNA vaccines, comments on the success of DNA vaccines currently in clinical trials. "A number of DNA vaccines are undergoing Phase I and IIa human trials at present, involving hundreds of human volunteers and so far have demonstrated that DNA vaccines are safe, well tolerated and capable of inducing both

humoral and cellular immune responses." (Galloway and Baillie, *Expert Opin. Biol. Ther.*, 4:1661-67, (2004) at page 1663.) Additionally, Galloway states that "[t]he effectiveness of ballistic delivery (gene gun) and cationic lipid formulations suggests that it is indeed possible to develop modalities that ***ensure*** efficient DNA uptake and effectively stimulate the primate immune response. (Galloway at page 1665 (emphasis added).)

Furthermore, the Leppla reference provides no data which disproves or calls into question the enablement of Applicant's invention. Leppla *et al.* presents technical issues to be considered when developing an anthrax vaccine, however, these issues do not mean that claimed invention is unpredictable or not enabled.

Applicant respectfully reminds the Examiner that the proper standard for compliance with enablement, scope of enablement, is not *absolute predictability* but *objective enablement*; evidence need not be *conclusive* but merely *convincing*. Accordingly, Applicant submits that the compelling animal data presented in the specification is sufficiently convincing that one of ordinary skill in the art would not doubt the feasibility of the claimed invention. Moreover, the *in vivo* successes documented in the Examples of the instant specification, *e.g.* Examples 10-13, clearly outweigh any speculative allegations of unpredictability asserted by the Examiner.

According to the Examiner's apparent view of the scope of enablement requirement, an applicant would have to submit conclusive data from human clinical trials in order to adequately enable a method of treatment applicable to humans. This is clearly in conflict with the statute, the rules and the guidelines of the M.P.E.P. Specifically, under the current case law, clinical efficacy is not required to show that a

therapeutic process is operable. As stated in M.P.E.P. § 2107.01, the "courts have found utility for therapeutic inventions, despite the fact that an applicant is at a very early stage in the development of a therapeutic regimen" or that a therapeutic treatment regimen is not at a stage where it is ready to be practiced on humans. *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

It is not within the province of the USPTO to require proof of efficacy in animals to grant a patent including claims to therapeutic methods. The PTO guidelines, in fact are explicit on this point: "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders." (M.P.E.P. § 2107.03). The guidelines further state that "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law, and in quoting *In re Brana*, *supra*, that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws". *Id.* In fact, all that is required by the patent laws is that a "*reasonable correlation*" exist between the scope of the claims and the scope of enablement. Citing to M.P.E.P. § 2164.02, "'correlation' as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless the Examiner has evidence that the model does not correlate. *In re Brana, supra* at 1566. Since the initial burden is on the Examiner to give reasons for lack of enablement, the Examiner must also give reasons for a

conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. As stated in *Cross v. Iizuka*, *supra*, at 1050, a rigorous or an invariable exact correlation is not required.

The references cited by the Examiner and arguments set forth do not cast doubt on the feasibility of the claimed invention in light of the data presented in the specification. Indeed, the captioned application describes various *in vitro* assays known in the art which sufficiently correlate to *in vivo* anthrax challenge experiments, *e.g.* at paragraph [0155] of the specification. The specification also describes data for various vaccine compositions in three different animal models. (*See* Examples 10-13 and 15.) Furthermore, the captioned application contains data showing that DNA vaccines containing codon optimized polynucleotides encoding anthrax antigens can provide protective immunity in rabbits. (*See* Example 13.) Finally, post-filing art, co-authored by the inventor of the captioned application, reports that the rabbit studies described herein resulted in product selection, pre-clinical safety studies, and U.S. FDA Investigational New Drug allowance. "A cationic lipid-formulated plasmid DNA vaccine confers sustained antibody-mediated protection against aerosolized anthrax spores." (*See* Hermanson, *et al. Proc. Natl. Acad. Sci.* 101:13601-13606, 1306 (2004).) Applicant asserts that a reasonable correlation thus exists between the data provided in the captioned application and the claimed methods.

Thus, given the explicit disclosure of specific *in vivo* working examples, using models that reasonably correlate to mammals, as noted in paragraph [0155] of the specification, Applicants respectfully submit that one skilled in the art would be able to

make and use the claimed invention without undue experimentation. Applicant respectfully asserts that this rejection be withdrawn.

For the reasons given above, Applicant submits that the scope of the present claims is commensurate in scope with the enablement provided in the present specification. The considerations listed by the Examiner are either resolved by the teachings in the specification or would have required only routine experimentation by one of skill in the art to practice the claimed invention. Accordingly, Applicant requests reconsideration and withdrawal of the scope of enablement rejection in view of the amendments to the claims and the remarks herein.

Rejections under 35 U.S.C. § 103

New - Claim Rejection - Allegedly Necessitated by Amendment of September 11, 2006

The Examiner has rejected claims 215-292 under 35 U.S.C. § 103(a) as being unpatentable over Lee *et al.* (U.S. Pat. App. No. 2004/0009945, publication date January 15, 2004, effective filing date July 10, 1998); Nagata *et al.* (Biochemical Biophysical Research Comm. 1999, Vol. 261, No. 2, pages 445-451; hereinafter "Nagata") and Hartikka *et al.* (Vaccine 2001, Vol. 19, pages 1911-1923; hereinafter "Hartikka"). (OA at pages 16-19.) More specifically, the Examiner stated that Lee *et al.* emphasize that it would be routine "to optimize codon expression for a particular host," and that the reference also "contemplate using pharmaceutical carrier to deliver disclosed nucleic acid composition for eliciting immune response in a subject." (OA at page 16.) According to the Examiner Nagata *et al.* "suggest that DNA immunization using the gene codon-optimized to mammals through the entire region is very effective." (OA at page 17.) The Examiner asserts that "at the time the claimed invention was made, use of cationic lipid to deliver compositions to elicit immune response was routine in the art," citing Hartikka *et al.* Applicants respectfully traverse this rejection.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, (Fed. Cir. 2006) "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) (*See* MPEP § 21430.01.) It is not permissible to use the present specification as the blueprint for this hindsight picking and choosing the isolated elements of each

reference, one of ordinary skill in the art would have found no specific suggestions to include one element and exclude another from each of the cited references to produce the presently claimed invention. The Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention.

Additionally, in order to support a *prima facie* case of obviousness, the prior art must suggest making the *specific* molecular modifications necessary to achieve the claimed invention. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). That is, simply because "one can conceive a general process in advance for preparing an *undefined* compound [*e.g.*, a codon optimized polynucleotide encoding the protective antigen of *B. anthracis*] does not mean that a claimed *specific* compound [*e.g.*, a polynucleotide encoding a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4 which has been codon optimized in a manner specified in independent claims 215, 231, 245, 261 and 275] was precisely envisioned and therefore obvious." *Deuel* at 1559. Thus, in order for cited references to be suitable as primary references upon which to base a *prima facie* case of obviousness, there must be, at a minimum, a teaching or suggestion in these references that would have compelled one of ordinary skill in the art to codon optimize a polynucleotide encoding SEQ ID NO:4 as claimed. Especially in view of the numerous potential polynucleotides which could encode for SEQ ID NO:4 and the numerous potential ways to codon optimize the polynucleotides. Therefore, the cited references taken together are seriously deficient

(particularly in view of the holding in *Deuel*), and cannot support a *prima facie* case of obviousness.

Independent claims 215, 231, 245 and 261, from which all other method claims depend, recite a method for treating or preventing anthrax infection in a vertebrate "comprising administering to a vertebrate in need thereof a composition comprising a carrier, a lipid GAP-DMORIE, a co-lipid and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4." Applicant asserts that Lee *et al.* does not teach or suggest the administration of a polynucleotide encoding a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4 and codon optimized, as set forth in claims 215, 231, 245, 261 and 275, in combination with the lipid GAP-DMORIE and a co-lipid nor do they suggest or disclose the specific codon optimization recited in the claims.

Hartikka *et al.* does not cure the deficiencies of Lee *et al.* Hatikka *et al.* discloses the injection of mice using Vaxfectin formulated with pDNA encoding influenza nucleoprotein (NP). (Abstract, page 1911) "The mechanism by which Vaxfectin enhances the antigen-specific antibody response is unclear." (page 1921, column 1, 2nd paragraph.) "Experiments are underway to further characterize the critical features of the Vaxfectin-derived response, and to expand the scope of the application of Vaxfectin adjuvancy for pDNA vaccines to other antigens, tissues, routes of administration and target species." (page 1921, column 2, last paragraph.) Thus, the ordinary artisan after reading Hartikka *et al.* would not have had an expectation of success in using other antigens because the authors clearly indicate that further studies are needed. Additionally, Hatikka *et al.* does not teach or suggest the administration of a codon-

optimized polynucleotide encoding a polypeptide at least 97% identical to SEQ ID NO:4.

Nagata *et al.* does not cure the deficiencies of Lee *et al.* Indeed, Nagata *et al.* discloses the use of a gene encoding amino acid residues 91 to 99 of listeriolysin O (LLO) derived from *Listeria monocytogenes*. The gene was codon optimized for mouse and then used to immunize mice via the gene-gun delivery method. Nagata *et al.* does not teach or suggest the administration of a codon-optimized polynucleotide encoding a polypeptide at least 97% identical to SEQ ID NO:4 administered to a vertebrate in a composition comprising GAP-DMORIE and a co-lipid as claimed.

As such, the combined references cited by the Examiner do not teach or suggest the claimed methods, let alone provide motivation for the combination or a reasonable expectation of success. Therefore, Applicant respectfully requests withdrawal of the rejection as it relates to the currently pending claims.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objection and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Elizabeth J. Haanes, Ph.D.
Attorney for Applicant
Registration No. 42,613

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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